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Movement disorder phenotypes in children with 22q11.2 deletion syndrome

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22q11.2 deletion syndrome (22q11.2DS) is associated with a broad spectrum of clinical phenotypes, including congenital heart defects and immune deficiencies. In addition, there is also an increased risk of psychiatric disorders, cognitive deficits and motor functional impairments [1–3]. To date, a systematic examination of movement disorders has not been undertaken in this group.

Nineteen participants with 22q11.2DS (11M:8F, median age=12.7 years, range=6.8–17.1), and 13 sibling controls (7M:6F, median age=11.2 years, range=7.5–17.5) were recruited following informed consent, via ongoing cohort studies at Cardiff University (CU) with no further selection criteria applied. Ethical approval was provided by CU School of Medicine Research Ethics (ref:17/69). The presence of the 3Mb 22q11.2 deletion was confirmed using the Infinium PsychArray-v1.1 (Illumina) platform, fluorescence in-situ hybridisation or genetic arrays through NHS medical genetics departments.

Data collected included: sex, age at examination, medical co-morbidities, and developmental history alongside assessment of full-scale IQ, psychiatric symptoms and coordination performance. Motor assessment involved a standardised videotaped clinical examination using a modified Burke-Fahn-Marsden Dystonia rating scale protocol[4]. Examinations were reviewed independently by three neurologists, blinded to all clinical information. Reviewers indicated if a movement disorder was observed and determined its phenomenology and body distribution. A movement disorder was considered present when there was agreement between all neurologists. Statistical analysis was carried out in R, using Fisher's exact tests, Pearson's correlations and t-tests as appropriate.

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Statistical Analysis: undertaken by ACC and KJP (both Cardiff University, UK).

Sample demographics are presented in Table 1. There was a higher rate of movement disorders in the 22q11.2DS group compared to controls (p=0.0002), with consensus agreement for a movement disorder in 18/19 (94.7%) children with 22q11.2DS compared to 4/13 (30.8%) of controls. Dystonia was the most common movement disorder subtype, in isolation (94.4%, n=17) and combined with upper limb distal jerks (5.6%, n=1). The limbs and cranio-cervical region were most commonly affected, with upper limb involvement in all 18 cases (Videos 1–3). Three of four controls displayed isolated dystonia, with upper limb involvement in all four. In the 22q11.2DS cohort, dystonia severity was mild (mean BFMDRS=24.93/120) but was associated with lower IQ (p=0.03, r=−0.52) and higher anxiety symptoms (p=0.03, r=0.57).

This is the first cohort study investigating the prevalence and type of movement disorders in young people with 22q11.2DS. Dystonia was the most commonly observed subtype, although these features were mild and tended to be associated with action. Identification of true movement disorders is often challenging in this age range, but the frequency of dystonic signs in the 22q11.2DS group indicate that they were associated with the 22q11.2DS phenotype, rather than neuro-motor immaturity. More severe dystonia was associated with lower IQ and higher levels of anxiety. The 22q11.2DS is known to affect brain development[5,6] and genes in the region such as COMT, are expressed in the brain[7]. Our study is cross-sectional, longitudinal examination throughout childhood, adolescence and into adult-life is required to gain more comprehensive understanding of the 22q11.2DS motor phenotype. Although this cohort is relatively small, the high rate and preponderance of dystonia indicate that it is likely part of the neurodevelopmental phenotype of 22q11.2DS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendices

Author Contributions

Name	Location	Role	Contribution
Adam C Cunningham	Cardiff University, United Kingdom	Author	Major role in the acquisition of data; Interpreted the data; drafted the manuscript for intellectual content
Wilson Fung	Cardiff University, United Kingdom	Author	Major role in the acquisition of data; revised the manuscript for intellectual content.
Thomas H Massey	Cardiff University, United Kingdom	Author	Major role in the acquisition of data; revised the manuscript for intellectual content.
Jeremy Hall	Cardiff University, United Kingdom	Author	Interpreted the data, revised the manuscript for intellectual content.
Michael J Owen	Cardiff University, United Kingdom	Author	Interpreted the data, revised the manuscript for intellectual content.
Marianne B M van den Bree	Cardiff University, United Kingdom	Author	Design and conceptualised study; interpreted the data, revised the manuscript for intellectual content.
Kathryn J Peall	Cardiff University, United Kingdom	Author	Design and conceptualised study; analysed the data; drafted the manuscript for intellectual content.

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Table 1:

Cohort demographic, motor and non-motor characteristics

	22q11.2DS	Sibling Controls	22q11.2DS vs. Sibling Controls	22q11.2DS cohort: Correlation analysis with BFMDRS Severity Scores
	n (%)/mean (SD)	n (%)/mean (SD)	p-value (95% CI)	Correlation coefficient (r)(p-value)
Total cohort (M: F)	19 (11: 8)	13 (7: 6)	–	
Age at Examination (years) (Median (range))	12.70 (6.8–17.1)	11.12 (7.5–17.5)	0.79 (−2.8, 2.2) *	−0.24 (0.34)
FSIQ	78.83 (10.06)	109 (15.13)	**<0.0001 (21.16, 39.64)** *	**−0.52 (0.03)**
BFMDRS severity score (maximum possible score = 120)	24.93 (8.17)			
Medication				
≥1 medication prescribed	12 (63.2%)	0 (0%)	**0.0004α**	
Melatonin	5 (26.3%)	-	-	
Antibiotics	4 (21.1%)	-	-	
Laxatives	3 (15.8%)	-	-	
Vitamin/Mineral Supplementation	3 (15.8%)	-	-	
Anti-depressants	1 (5.3%)	-	-	
Medical Co-morbidities				
Cardiac Defect	13 (68.4%)	0 (0%)	**0.0001**$^{\alpha}$	
ASD/VSD	5 (26.3%)	-	-	
Tetralogy of Fallot	4 (21.1%)	-	-	
Other	4 (21.1%)	-	-	
Past/Present Seizures	1 (5.3%)	0 (0%)	>0.99$^{\alpha}$	
Cleft lip/palate	6 (31.6%)	0 (0%)	0.06$^{\alpha}$	
Recurrent Respiratory Infections	7 (36.8%)	0 (0%)	**0.02**$^{\alpha}$	
Recurrent Ear Infections	6 (31.6%)	1 (7.7%)	0.20$^{\alpha}$	
Psychiatric Symptoms				
ADHD	7 (36.8%)	1 (7.7%)	0.10$^{\alpha}$	

	22q11.2DS	Sibling Controls	22q11.2DS vs. Sibling Controls	22q11.2DS cohort: Correlation analysis with BFMDRS Severity Scores
Anxiety Disorder (Overall)	5 (26.3%)	1 (7.7%)	0.36[α]	
Social Phobia	3 (15.8%)	0 (0%)	0.25[α]	
Generalised Anxiety Disorder	1 (5.3%)	0 (0%)	>0.99[α]	
Specific Phobia	1 (5.3%)	1 (7.7%)	>0.99[α]	
ADHD Count Score	3.39 (3.38)	1.00 (3.16)	0.07 (−2,39, 1.3)[*]	0.41 (0.10)
Anxiety Count Score	2.13 (3.18)	1.75 (2.96)	0.78 (−3.17, 2.42)[*]	**0.57 (0.03)**
Autism Trait Symptoms Score	11.43 (5.16)	2.50 (2.27)	**<0.0001 (−12.55, −5.30)**[*]	0.42 (0.16)
Developmental History				
Pre-term Birth	4 (21.1%)	5 (38.5%)	0.43[α]	
Failure to thrive	8 (42.1%)	0 (0%)	**0.01**[α]	
Feeding Difficulties	16 (84.2%)	1 (7.7%)	**<0.0001**[α]	
Parental Reported Clumsiness	15 (78.9%)	3 (23.1%)	**0.003**[α]	
Talking by 2 years of age	6 (31.6%)	12 (92.3%)	**0.0009**[α]	
Walking by 1.5 years of age	11 (57.9%)	11 (84.6%)	0.14[α]	
Statement of educational needs/Education and health care plan	13 (68.4%)	1 (7.7%)	**0.0009**[α]	
Age at riding a bike (years) (Median (range))	6.5 (5–10)	5 (3.5–7)	0.09 (−27.6, 2.1)[*]	0.02 (0.95)
Age at being able to buttons (years) (Median (range))	6.2 (3.5–10.25)	4 (3–6.5)	**0.008(−41.6, −7.0)**[*]	−0.10 (0.79)
Age at being able to do laces (years)(Median (range))	9.75 (6–11)	6.9 (5–8.7)	**0.008 (−47.3, 8.4)**[*]	0.20 (0.63)
Movement Disorder				
Evidence of movement disorder on examination	18 (94.7%)	4 (30.8%)	**0.0002**[α]	
Dystonia	17 (94.4%)	3 (23.1%)	**0.0002**[α]	
Distal UL jerks (Possible myoclonus/possible Chorea)	1 (5.6%)	1 (7.7%)	>0.99[α]	
Body Part Affected				
Eyes	0 (0%)	0 (0%)	>0.99[α]	

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	22q11.2DS	Sibling Controls	22q11.2DS vs. Sibling Controls	22q11.2DS cohort: Correlation analysis with BFMDRS Severity Scores
Oromandibular Region	6 (31.6%)	0 (0%)	**0.03**$^{\alpha}$	
Cervical	8 (42.1%)	1 (7.7%)	**0.05**$^{\alpha}$	
Upper Limbs	18 (94.7%)	4 (30.8%)	**0.0002**$^{\alpha}$	
Trunk	0 (0%)	0 (0%)	>0.99$^{\alpha}$	
Lower Limbs	8 (42.1%)	3 (23.1%)	0.45$^{\alpha}$	
DCDQ Scores				
Overall	37.37 (12.54)	69.75 (6.90)	**<0.0001 (24.27, 40.49)***	−0.29 (0.24)
Control During Movement	15.21 (5.35)	28.17 (2.89)	**<0.0001 (9.51, 16.4)***	−0.11 (0.65)
Fine Motor Score	10.95 (3.63)	19.33 (1.44)	**<0.0001 (6.13, 10.64)***	−0.41 (0.09)
General Co-ordination Score	11.21 (5.34)	22.25 (3.98)	**<0.0001 (7.4, 14.7)***	−0.29 (0.23)

Key: ADHD: Attention Deficit Hyperactivity Disorder, DCDQ: Developmental Co-ordination Disorder Questionnaire, FSIQ: Full Scale Intelligence Quota, SCQ: Social Communication Questionnaire, UL: Upper Limbs. Control during movement, fine motor score and general co-ordination score all form sub-sections of the DCDQ. The SCQ is used to measure Autism Trait Symptom Score, ADHD and Anxiety symptoms were measured using the child and adolescent psychiatric assessment (CAPA). **Bold** denotes p-value ≤0.05,

*denotes statistical comparison using unpaired t-test,

$^{\alpha}$denotes comparison using chi-square test,

-denotes no value or no statistical analysis undertaken.

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